REMARKS

This amendment is submitted in response to the Advisory Office Action mailed November 26, 2008, and is responsive to the Office Action dated January 2, 2008.

The Pending Claims

Claims 1-26, as amended, and new claim 27, remain pending. New claim 27 has been added to cover a preferred embodiment of the invention. Claims 4, 8-12, 16 and 18-26 are withdrawn. Applicants understand that these claims will be rejoined and allowed once the pending claims are allowed. The claims have been amended as set forth herein, but no new matter is introduced by these amendments or by the presentation of the new claim. Therefore, they all should be entered at this time.

To correct a minor clerical error in claims 13, 14, and 16, the article "a" has been changed to the article "the." In claim 14, the term "expression" is inserted before the term "vector."

Applicants submit that the objections and rejections based on non-statutory subject matter, indefiniteness, lack of enablement and anticipation are overcome in light of the amendments and arguments presented in the response.

Accordingly, entry of these amendments is respectfully requested.

Rejection Under 35 U.S.C. §101

Claim 17 was rejected under 35 U.S.C. §101, as being directed to non-statutory subject matter. Applicants have amended the claim, which now recites "an isolated polynucleotide comprising SEQ ID NO:38." Withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 1-2, 5-7 and 13-15 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants have amended claim 1 by (1) substituting the term "polynucleotide" (second occurrence) with the term "transcript;" (2) changing the plural form of "sequences" to its singular counterpart; (3) deleting the term "including; and (4) incorporating the phrases "wherein said 5'

intronic sequence includes" before the phrase "an in-frame methionine codon." Support for these amendments can be found at paragraphs [0014], [0015], [0018], [0019], [0021], and [0041].

With regards to claim 15, the dependency of this claim has been changed to claim 13 instead of claim 14. In addition, the phrase "transfected with the expression vector" has been inserted before the phrase "according to." Support for this amendment can be found at paragraphs [0063], [0095], [0096] and the Examples.

In light of these amendments and remarks, Applicants submit that the rejection is overcome and should be withdrawn.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1-3, 5-7, and 13-15 were rejected under 35 U.S.C. 112, first paragraph, for failure to comply with the enablement requirement. Applicants respectfully traverse the rejection.

At the outset, Applicants wish to point out that the absence of Jint-Jß2.1-Cß2 mRNA in an MBA-13 cell population is not an unexpected or inconsistent finding. This is because MBA-13 is not a cloned cell line. Instead, it is a cell strain that represents many cell types, which have been passaged in this manner for many cell generations. Therefore, long-term passaging of such cells causes selection of sub-populations, some of which may lack TCR. Further to the heterogeneity of the mesenchymal populations that may result in selection of one specific cell type following many passages, it should be kept in mind that mesenchymal (stromal) populations are highly plastic.

The plasticity of stem cells and mesenchymal cells is well known. In fact, one of the inventors, Dov Zipori, has addressed this issue in publications such as in "Cytokines Mol. Ther., 1996, 2(1):29-38, entitled "Control of Stroma-Dependent Hematopoiesis By Basic Fibroblast Growth Factor: Stromal Phenotypic Plasticity and Modified Myelopoietic Functions" (Appendix 1), and more recently, in the "Current Stem Cell Res. Ther., 2006, 1:95-102, entitled "The Stem State: Mesenchymal Plasticity As A Paradigm" (Appendix 2). Such plastic nature may account for variability in the behavior of cultured cells.

This, however, does not mean that primary cells isolated from the animal or human, when examined shortly thereafter, would be variable. To the contrary, such cells are relatively uniform. Indeed, most mesenchymal isolates, at first passages, are similar and one can, with great

certainty, say that any normal mouse strain or a human individual will harbor TCR in the mesenchyme. This is certainly the case for fresh tissues.

In addition, Applicants respectfully submit that the presently claimed invention does not require undue experimentation. Thus, to use Jint-Jß2.1-Cß2 or any other TCR sequence as disclosed in the present application, a skilled artisan would only have to ascertain the presence and type of TCR transcripts using a simple polymerase chain reaction (PCR) screen of the extracted mRNA, which, by itself, cannot reasonably be considered as undue experimentation. PCR screening is a simple, relatively low cost, extremely sensitive and ultra-rapid procedure and well known to one skilled in the art. For example, a skilled artisan who wishes to analyze a TCR type in a mesenchymal tissue or cell can simply use PCR screening. The use of PCR screening is exemplified in Examples 2, 3 and 5 of the published patent application.

With respect to the Carroll reference (Cell, 2000, 101(6): 577-580), Applicants note that this reference fails to describe or suggest T cell receptors, in contrast to the claimed invention. Instead, the Carroll reference discusses the evolution of morphological diversity and, more specifically, the importance of cis-regulatory DNA and transcription factors in this phenomenon. Functional diversity or diversity at the protein level are not addressed. Moreover, there is nothing in the Carroll reference that suggests that similar genes do not share a similar function across species.

With respect to the Office Action's assertion that the disclosure of approximately 30 other TCR transcripts were derived from database hunting, Applicants note that most known sequences are probably found in data banks as products of large scale sequencing projects, such as the Human Genome Project or as expressed sequence tags (EST). As mentioned above, a simple PCR screen is all that is needed to ascertain which, if any, TCR transcript is found in the mesenchymal cells of interest.

In view of the above remarks, Applicants respectfully submit that the claimed invention, as set forth in claims 1-3, 5-7 and 13-15, is enabled. Accordingly, the rejection of these claims under 35 U.S.C. §112, first paragraph, should be withdrawn.

Rejections Under 35 U.S.C. §102(b)

Claims 1, 2, 6, 7, 13 and 14 have been rejected under 35 U.S.C. 102(e), as being anticipated by U.S. Patent Application Publication No. 20020138081 to Olga Bandman

(hereinafter "Bandman"), as evidenced by Entrez Nucleotide Accession No. L34740 (http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nuccore&id=1100190), Entrez Nucleotide Accession No. AAA82787 (http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=protein&id=1100191), and IGc domain description (http://www.ncbi.nlm.nih.gov/structure/cdd/cddsrv.cgi?uid=28981). In particular, the Office Action asserts that the nucleotides 1-139 of SEQ ID NO: 67 of the present application is identical to the nucleotides 35-173 of SEQ ID NO: 130 of Bandman (hereinafter "the Bandman sequence"). Therefore, the Bandman sequence anticipates the instant claims. Applicants respectfully traverse this rejection as explained herein.

At the outset, Applicants respectfully submit that the claimed invention, as set forth in amended claim 1, is drawn to an isolated polynucleotide that includes a transcript of a T cell receptor (TCR) gene that lacks V region sequences and comprises (1) a constant (C) domain; (2) a joining (J) region sequence; and (3) a 5' intronic J sequence that is upstream to the J region sequence, wherein the5' intronic J sequence includes an in-frame methionine codon.

Contrary to the claimed invention, the Bandman sequence is distinct from and not identical to the claimed polynucleotide transcript. At this juncture, Applicants would like to point out a possible typographical error in the description of the nucleotide assignment for the Bandman sequence. As provided in the Office Action at page 16, the following nucleotide assignment for the Bandman sequence is as follows:

> "Residues 1-124: genomic region 5' of the human Jß2.3 exon;
> Residues 125-324: Jß2.3 exon - intron - Jß2.4 exon;
> Residues 325-1642: exon 1 - exon 2 - intron B - exon 3 - exon 4 - of the 4 exon Cß2 domain;
> Residues 1643-1186: genomic region 3' of exon 4 of the Cß2 domain."

As underlined above, there cannot be a residue number 1642 in a 1186-bp long polynucleotide so that the reference may be to 1043 or 1143. Regardless of the typographical error and in view of the alignment results, Applicants respectfully disagree with the Office Action's analysis of residues 325-1186.

By using the BLASTN sequence alignment program with residues 325-1186 of the Bandman sequence as Query and human germline TCR beta chain (accession number U66061)

as Subject, enclosed herein as Appendix 3, it can be seen that residues 325-1186 of Bandman contain only the structure: exon 1 - exon 2 - intron B - exon 3 - exon 4 - of the Cß2 domain, without the genomic region 3' of exon 4. The Bandman sequence does not even contain the entire exon 4, since the last nucleotide aligns with base 204439 of U66061 (enclosed as Appendix 4), which is 12 nucleotides before the end of exon 4 of the Cß2 domain, situated at base 204451. Moreover, the Bandman sequence even seems to lack the poly A signal, situated between bases 204446-204451 of U66061 (see Appendix 4).

When the Bandman sequence is translated into a protein sequence using the first in frame methionine codon as the start codon, the first 46 amino acids, which encode the 5' intronic sequence upstream of Jß2.3 and the Jß2.3 sequence itself, are identical to the first 46 amino acids of SEQ ID NO: 51, which is the polypeptide encoded by SEQ ID NO: 67. However, the sequences diverge thereafter and there are several stop codons at positions 100, 140, 144, 173, 177, and 294, as shown in the attached Appendix 5.

Furthermore, a translation map of the Bandman sequence and its nucleotide assignment, as shown in Appendix 5, shows that the Bandman sequence comprises two different Jß2 sequences (Jß2.3 and Jß2.4) that are separated by an intron sequence. It also shows the presence of multiple stop codons, as mentioned above and underlined in Appendix 5, the first of which is placed at the start of the C region sequence. The presence of the stop codon at this particular position in the Bandman sequence would cause the sequence to be untranslatable.

Moreover, there is no indication in the Bandman application that SEQ ID NO:130 was successfully expressed in an expression system or transfected into a mammalian cell host, contrary to the claimed polynucleotide transcript.

The differences between the claimed polynucleotide transcript and the Bandman sequence are summarized in the scheme below:

Claimed Polynucleotide transcript: 5' intronic sequence- J - C

↓ Translation

Translated into a truncated TCR: 5' intronic sequence- Jβ2.3 - Cβ2

Bandman's sequence: 5' intronic sequence- Jβ2.3 -intron- Jβ2.4 - Cβ2

↓ Translation

Untranslatable

In addition, the present application recites "... a transcript of a TCR gene...lacking V region sequences and comprising a C domain and joining (J) region sequences and a 5' intronic J sequences upstream...including an in-frame methionine codon." The Bandman sequence has multiple J sequences separated by an intron. This is not equivalent to the claimed polynucleotide transcript or to its expressed protein.

Based on the above discussion, Applicants respectfully submit that the Bandman sequence is either an artifact or an immature product that has yet to undergo the recombination event that selects one J gene during TCR processing.

Furthermore, the present claimed invention is drawn to TCR transcripts specifically related to the mesenchyme and their use for modulation of mesenchymal cell growth or for detection of mesenchymal cells. Claim 27 specifically recites the mesenchymal (stromal) origin of the TCR transcript. This further distinguishes the invention from Bandman, which describes a plurality of cDNAs expressed in vascular tissue and their use for diagnosis, monitoring and treatment of vascular disorders.

Based on the foregoing remarks, Bandman fails to anticipate the subject matter as set forth in amended claim 1, as well as in dependent claims 2, 6, 7, 13 and 14. Accordingly, Applicants respectfully request the withdrawal of this rejection.

CONCLUSION

For at least the reasons set forth above, this application is in condition for allowance. Favorable consideration and prompt allowance of the claims are earnestly requested. Should the

Examiner have any questions that would facilitate further prosecution or allowance of this application, the Examiner is invited to contact the Applicants' representative designated below.

Respectfully submitted,

12/2/08
Date

Allan A. Fanucci, Reg. No. 30,256

WINSTON & STRAWN LLP
Customer No. 28765

212-294-3311